HHS Public Access

Author manuscript

Nat Rev Nephrol. Author manuscript; available in PMC 2024 September 01.

Published in final edited form as:

Nat Rev Nephrol. 2024 March ; 20(3): 161–174. doi:10.1038/s41581-023-00778-x.

Clonal haematopoiesis, ageing and kidney disease

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Abstract

Clonal haematopoiesis of indeterminate potential (CHIP) is a preclinical condition wherein a sizeable proportion of an individual's circulating blood cells are derived from a single mutated haematopoietic stem cell. CHIP occurs frequently with ageing — more than 10% of individuals over 65 years of age are affected — and is associated with an increased risk of disease across several organ systems and premature death. Emerging evidence suggests that CHIP has a role in kidney health, including associations with predisposition to acute kidney injury (AKI), impaired recovery from AKI, and kidney function decline, both in the general population and among those with chronic kidney disease (CKD). Beyond its direct effect on the kidney, CHIP elevates the susceptibility of individuals to various conditions that can detrimentally affect the kidneys, including cardiovascular disease, obesity and insulin resistance, liver disease, gout, osteoporosis

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Author contributions

C.V. researched data for the article and wrote the manuscript. P.N., C.V., M.B.L. and T.N.K. made substantial contributions to discussions of the content. All authors reviewed or edited the manuscript before submission.

Competing Interests

P.N. reports research grants from Allelica, Apple, Amgen, Boston Scientific, Genentech / Roche, and Novartis, personal fees from Allelica, Apple, AstraZeneca, Blackstone Life Sciences, Foresite Labs, Genentech / Roche, GV, HeartFlow, Magnet Biomedicine, and Novartis, scientific advisory board membership of Esperion Therapeutics, Preciseli, and TenSixteen Bio, scientific co-founder of TenSixteen Bio, equity in Preciseli and TenSixteen Bio, and spousal employment at Vertex Pharmaceuticals, all unrelated to the present work. M.B.L. reports received speaking and advisory board fees from Bayer, Otsuka, Reata and Sanofi. The remaining authors declare no competing interests.

and certain autoimmune diseases. Aberrant pro-inflammatory signaling, telomere attrition and epigenetic ageing are potential causal pathophysiological pathways and mediators underlying CHIP-related disease risk. Experimental animal models have shown that inhibiting inflammatory cytokine signaling can ameliorate many of the pathological effects of CHIP, and assessment of the efficacy and safety of this class of medications for human CHIP-associated pathology is ongoing.

Introduction

Somatic mosaicism across body tissues is a recognized sequela of ageing across species.[1] Replicating cells in tissues acquire between 20 and 40 new mutations per year.[2] An acquired mutation that confers a selective advantage can lead to clonal expansion of the affected cell in its tissue locale, and organs can become a mosaic of cells with subtle variations in their DNA makeup over time. Uncontrolled, clonal replication of a cell that results from an acquired mutation in an oncogene or tumor suppressor gene is the main mechanism by which cancerous tumours arise.[3] However, somatic mosaicism is also observed in healthy tissue across organ systems[4–9], as well as non-cancerous and pre-cancerous states in the continuum of healthy to malignant tissue[10], including in VEXAS syndrome **[G]** [11], endometriosis[12] and clonal haematopoiesis.[13,14]

Haematopoiesis is the process whereby blood cells of the myeloid and lymphoid lineage are formed in the bone marrow (Figure 1a). These cells then go on to circulate in the bloodstream and, in some cases, take up residence in various tissues.[15] In physiological haematopoiesis, >20,000 haematopoietic stem and progenitor cells (HSPCs) contribute fairly evenly to blood cell production.[16] Clonal haematopoiesis (CH) occurs when blood cells production there is skewed and daughter cells arise from a single HSPC owing to selection and clonal expansion in the bone marrow (Figure 1b). Several types of CH have been described (Figure 1c), each characterized by the type of genetic change that drives clonality. The best-characterized genetically inferred type is CH of indeterminate potential (CHIP). CHIP occurs when a pathogenic point mutation, or small insertion or deletion in a gene associated with myeloid cancer, occurs in an HSPC that then contributes at least 4% of the cells in the circulating blood cell pool. The development of CHIP is a surprisingly common age-related process — at least 10% of individuals above 65 years of age were affected across studies (Figure 1d), which far exceeds the prevalence of myeloid cancers. Importantly, CHIP has been associated with greater non-oncologic disease burden across several organ systems and with mortality. Of note, CHIP is distinct from other types of CH, such as CH affecting lymphoid cancer-associated genes (termed *L-CHIP*[17]), and clonality caused by acquired structural change affecting regions or whole chromosomes (for example, mosaic X or Y chromosome loss), which are also commonly observed with ageing[18,19] and seem to contribute to systemic disease[20,21], but are less well understood.

In this Review, we focus on the role of CHIP as a determinant of the ageing trajectory, including its roles in kidney disease and related disorders, such as cardiovascular disease, obesity, diabetes, gout and osteoporosis. We also discuss progress in translating these mechanistic insights into therapies for preventing or treating CHIP, and other considerations for integrating CHIP into clinical practice.

Ageing of the cellular immune system

The main function of the immune system is to recognize and eliminate organismal threats, including invading pathogens but also cancerous, senescent or injured cells. These immune-coordinated processes are crucial to maintaining organ homeostasis, including in the kidney.[22,23] White blood cells of the innate and adaptive immune systems undergo degenerative changes with age (also termed immunosenescence), which can predispose individuals to infection and certain chronic and autoimmune diseases. Age-related changes in adaptive immune cells include a relative decrease in naïve lymphocyte populations, and conversely, a relative increase in memory and memory-like lymphocyte populations.[24] Compared with naive cells, aged mature T cells have a more restricted receptor repertoire that limits their ability to respond to new antigens[25], and mature B cells have an analogous restricted plasticity in their humoral responses owing to defective antibody class switch recombination and decreased somatic hypermutation.[26] Innate immune cells of the myeloid lineage such as monocytes, macrophages, neutrophils and dendritic cells also display age-related dysfunction, with global impairments in the recognition of threat signals (that is, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs)), in the ability to perform phagocytosis, and in the regulation of the production of cytokines and other effector proteins.[24] Several studies have identified an age-associated constitutive systemic elevation in levels of several pro-inflammatory cytokine, such as IL-6, IL-1β and tumour necrosis factor (TNF), which has been termed “inflammageing”.[27] These basal elevated cytokines derive from many sources[28], including adipose tissue-infiltrating macrophages that, along with other tissue-resident and tissue-infiltrating macrophage populations, adopt an increasingly inflammatory phenotype with age.[27] Age-related immunosenescence and inflammageing cumulatively predispose older individuals to infections, chronic organ damage and death.[27–29]

The timeline of immune system ageing varies between individuals[16], and CHIP is a novel factor believed to contribute to accelerated immune ageing. First, CHIP mutations generally skew HSPCs toward producing more myeloid than lymphoid daughter cells[30–33], a cardinal feature of an ageing bone marrow system.[34–36] Consequently, CHIP mutations disproportionately affect myeloid cells in circulation, and their effects on cells of this lineage have been the best characterized and implicated in disease pathology to date. For example, monocytes, dendritic cells, and tissue-resident macrophages with CHIP mutations produced more proinflammatory cytokines than non-mutated cells in several studies[32,37–45], plausibly because the genes affected regulate cytokine production directly.[46,47] CHIP mutations also impair neutrophil functions, leading to reduced phagocytosis and formation of extracellular traps.[48] Our understanding of the effect of CHIP on cells of the lymphoid lineage is limited; in these cells, other types of CH such as mosaic chromosomal structural changes (Figure 1c) seem to be more important.[17,49]

Overall, the effects of CHIP on the immune system — particularly on cells of the innate and myeloid lineages — mirror and might exacerbate known age-associated degenerative changes. CHIP and ageing are intrinsically linked: age is the main epidemiological risk factor for CHIP, and chronic inflammation — as observed in inflammageing — is a key driver of CHIP clonal growth in the experimental setting.[50–55] However, extensive evidence

(discussed below) indicates that CHIP is an independent source of immune-mediated morbidity and mortality and is not a mere marker of an unhealthy ageing trajectory.

CHIP within the spectrum of myeloid disease

According to 2022 World Health Organization and International Consensus Classification guidelines[56,57], CHIP is defined as the presence of a clonal cell population harbouring somatic mutations in myeloid malignancy-associated genes that is detected in the blood or bone marrow at a variant allele fraction **[G]** (VAF) of ≥ 2% (that is, in ≥4% of circulating diploid blood cells) in individuals without a diagnosed haematologic disorder or unexplained cytopenia. In cases of concurrent cytopenia attributable to the CHIP mutation without significant dysplasia or neoplasia, clonal cytopenia of undetermined significance (CCUS) is the best descriptor.[58] CHIP and CCUS are considered pre-malignant states for myeloid cancers such as acute myeloid leukemia (AML), myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs; Figure 2). However, the absolute risk of transformation to myeloid cancers is low — between 0.03 and 1% of cases transform to overt myeloid cancer per year.[58,59] This relationship between CHIP and myeloid cancer risk is comparable to the relationship between monoclonal gammopathy of undetermined significance (MGUS) and transformation to plasma cell myeloma (0.5–1% annual incidence).[60–62] The CH Risk Score (CHRS) is a new tool that enables individual risk stratification for cancer progression based on individual age, routine clinical laboratory values, and the number and size of CHIP clones.[63]

Detecting CHIP in the blood

CHIP is detected using next-generation sequencing (NGS) methods that probe myeloid cancer-associated genes for specific mutations (Supplementary Table 1). Targeted gene panels, whole exome sequencing (WES) or whole genome sequencing (WGS) strategies can be used to detect CHIP. Several technical considerations are relevant to CHIP sequencing methods and variant interpretation (discussed in detail elsewhere[59]). Importantly, CHIP variant detection involves three major steps. First, DNA from peripheral blood cells is sequenced using NGS. Second, the aligned sequencing data is run through a somatic variant calling pipeline; this step generates a list of putative acquired variants in the sample(s) within the specified genes. Finally, this list is filtered to remove variants with low sequencing depth or other signs of poor sequencing quality, as well as suspected sequencing artifacts, germline variants and passenger variants **[G]**. The goal is to produce a curated list of pathogenic somatic variants that correspond to CHIP[59]. The sensitivity of CHIP detection depends on the NGS method used; methods with lower average sequencing depth are less sensitive. WGS or WES methods typically have an average of 50 sequencing reads per site, whereas targeted sequencing methods typically achieve ≥500 reads per site. Since at least three variant sequencing reads are required to call CHIP, WGS will not detect CHIP variants with VAF smaller than 6% (3/50) on average, whereas targeted sequencing enables detection of smaller CHIP clones.[64] Given these differences in sensitivity, the prevalence of CHIP and the magnitude of its effects reported in research studies should be interpreted in the context of the type of sequencing methodology used to detect CHIP. Targeted sequencing methods can also detect CHIP mutations below the diagnostic threshold for CHIP (that is, VAF <2%), but the terminology for this entity and its prognostic relevance are unclear.

In practical terms, research studies pertaining to CHIP typically either mine existing WGS and WES data for CHIP variants or, if this option is not available for a cohort of interest (or if greater sequencing depth is desired), samples can be sequenced on more cost-effective targeted panels. Similarly, CHIP is sometimes detected incidentally in WES, WGS or sequencing of blood cell-free DNA performed in the clinical setting[65], whereas targeted panels are typically used for prospective identification. Of note, DNA microarray genotyping, which is available for many historical research cohorts, can be used to detect a limited set of CHIP hotspot mutations that have been directly genotyped on genome-wide genotyping arrays.[66]

Across studies, ~75% of CHIP variants are detected in 1 of 3 genes: *DNMT3A*, *TET2*, *ASXL1*.[14,59,64] These genes encode proteins with primary roles in epigenetic regulation. DNMT3A is one of two enzymes that performs *de novo* methylation of DNA CpG sites. DNMT3A coordinates the bulk of dynamic methylation changes that occurs throughout the body after the embryonic phase of life, and has a crucial role in regulating gene expression and several other cellular processes.[67] The most common *DNMT3A* mutation — and the most common CHIP mutation overall — is a missense mutation at the R882 position, which is the main residue that makes contact with the DNA backbone during methylation.[67,68] Several other truncating and missense mutations in *DNMT3A* have been reported in CHIP (Supplementary Table 1), but the other *de novo* methyltransferase (DNMT3B) has not been implicated in CHIP. The second most common CHIP gene, *TET2*, encodes an enzyme involved in demethylation of DNA CpG sites. Both DNMT3A and TET2 have roles in processes other than DNA methylation that are important in CHIP pathogenesis. For example, TET2 is a co-factor for a histone deacetylase (HDAC2) that mediates chromatin silencing of the key proinflammatory cytokine IL-6.[46] Furthermore, DNMT3A and TET2 are part of a transcription factor complex that permits the expression of transcription factor A mitochondrial (*TFAM*), and inactivating CHIP mutations in *TET2* and/or *DNMT3A* lead to mitochondrial genomic instability and a cascade of inflammatory signaling.[47] The third most common CHIP gene, *ASXL1*, is part of the polycomb repressive complex 2 (PRC2) that mediates histone H3 lysine 27 (H3K27) trimethylation, which is a repressive epigenetic mark.[69] Loss-of-function mutations in *ASXL1* in HSPCs are associated with a global loss of H3K27 methylation.[69] Mutations in other core members of the PRC2 complex — *EZH2*, *SUZ12* and *EED* — are also noted in CHIP[14], albeit much less frequently than mutations in *ASXL1*.

Other genes commonly affected in CHIP include the DNA-damage response (DDR) regulators *PPM1D* and *TP53*. These mutations are classically observed in individuals that have received chemotherapy for solid organ cancers and are thus sometimes referred to as treatment-related CH (t-CH)[70], although these mutations are also noted in individuals without this clinical history. Mutations in splicing factors such as *SF3B1*, *SRSF2* and *U2AF1* are also noted to drive CHIP, but tend to occur later in life and have faster clonal expansion rates than the aforementioned mutations.[71] The *JAK2* V617F hotspot mutation, which is noted most cases of overt myeloproliferative neoplasms[72], is also a recurrently observed CHIP driver mutation.[59,64]

Consequences of CHIP on human health

CHIP has been associated with the incidence and severity of a broad array of medical conditions, spanning several organ systems, and is associated with a 40% increased risk of all-cause mortality.[14,59] Below we highlight the current state of knowledge as it relates to the effects of CHIP on the kidneys, including its implications in chronic kidney disease (CKD), acute kidney injury (AKI), and conditions that impact kidney health such as diabetes and cardiovascular disease. We also detail known mechanisms underlying these associations and highlight the importance of pro-inflammatory pathway upregulation (Box 1). These insights have been ascertained from *in vitro* and murine experiments, single-cell RNA sequencing analyses and human genetic studies.

CHIP and the kidneys—CHIP has been associated with kidney functional impairment both in the general population and in the setting of CKD, as well as with a higher risk of AKI. One study first showed that CHIP correlated with lower cystatin-C-based estimated glomerular filtration rate (eGFR) in the UK Biobank, which is a general population cohort.[73] We then showed that CHIP was associated with an increased risk of incident 30% reduction in eGFR (hazard ratio (HR) 1.17, 95% confidence interval (CI): 1.01–1.36) over a median follow-up period of 8 years in a meta-analysis of three population-based cohorts, and the risk did not differ based on baseline CKD status.[74] A 2022 single cohort examined rarer subtypes of CHIP (that is, CHIP driven by *JAK2* or *CALR* mutations), and found that CHIP driven by *CALR* mutations was associated with kidney function decline.[75] The aforementioned CHRS, which grades the likelihood of progression of CHIP to myeloid malignancy, also correlates with the risk of incident non-malignant outcomes in the UK Biobank, including incident CKD. Specifically, a low-risk CHIP clone is associated with a 33% higher risk of CKD (HR 1.33, 95% CI 1.23–1.43), whereas a high-risk CHIP clone is ascribed a six-fold higher risk (HR 5.99, 95% CI 4.34–8.28).[63]

A few studies have examined CHIP and outcomes among individuals with existing CKD. Our study examined 162 individuals with all-cause CKD (mean eGFR 27.4 ml/min/1.73m^2) and found that CHIP was associated with a 2-fold increased risk of kidney failure or 50% eGFR decline (HR 2.2, 95% CI 1.2–3.8).[76] A second nested case-control study examined 294 individuals with diabetic kidney disease and did not report an association with kidney function decline.[77] This lack of association might be specific to diabetic kidney disease, although the variant curation procedures used could have also biased the results towards the null hypothesis.[78]

CHIP has been associated with an increased risk of AKI and impaired recovery from AKI.[79] First, in three population-based cohorts (n = 442,153 individuals), we showed that CHIP is associated with a 26% greater risk of AKI (HR 1.26, 95% CI 1.19–1.34) and a 65% higher risk of severe AKI requiring dialysis (AKI-D) (HR 1.65, 95% CI 1.24–2.20). CHIP driven by mutations in CHIP genes other than *DNMT3A* (that is, non-*DNMT3A* CHIP) was associated with an even greater risk of these outcomes (HR 1.49, 95% CI 1.37–1.61 for AKI; HR 2.18, 95% CI 1.51–3.15 for AKI-D). An ancillary analysis of individuals hospitalized with AKI in the *ASSESS-AKI* cohort study[80], showed that non-*DNMT3A* CHIP and large CHIP clones (VAF ≥ 10%) were associated with a non-resolving AKI pattern (adjusted

odds ratio (OR) 2.30, 95% CI 1.14–4.64 for non-DNMT3A CHIP; 2.49, 95% CI 1.02–6.07 for large CHIP clones). Large CHIP clones were additionally associated with long-term impaired kidney function, with a nearly tripled risk of incident kidney failure or 50% eGFR decline over 5 years (HR 2.93, 95% CI 1.08–7.96).

CHIP has also been associated with kidney injury and damage in mouse models. CHIP mouse models generally involve a bone marrow transplant (BMT) of HSPCs with a classical CHIP mutation such as a truncating mutation in *Dnmt3a* or *Tet2*. One method entails transplanting a chimeric donor HSPC pool constituted of 10–20% mutated HSPCs and 80–90% wild-type HSPCs versus 100% wild-type HSPCs in a mouse that has undergone lethal irradiation of its native bone marrow (Figure 3a).[81] The mice used in these models typically have other genetic modifications and/or undergo environmental (for example, dietary) exposures to accelerate a desired clinical outcome or surrogate. For example, to study CHIP and atherosclerosis, *Tet2*-chimeric bone marrow has been transplanted into atherosclerosis-prone mice (that is, mice with low-density lipoprotein receptor mutations ($Ldlr^{-/-}$) fed a high-fat, high-cholesterol diet).[38,39] A study characterizing atherogenic *Tet2*-CHIP mice provided the first mouse model evidence of potential CHIP involvement in the kidney. Specifically, *Tet2*-CHIP mice had greater macrophage infiltration in the kidneys and glomerulosclerosis than control mice in an atherogenic model.[38] In a subsequent study evaluating the role of CHIP in the response to chronic renin–angiotensin–aldosterone system activation, mice receiving a BMT of inactivating mutations in *Tet2* or *Dnmt3a*, as well as an angiotensin II infusion, had greater cardiac and kidney fibrosis than control mice.[40] A subsequently developed technique for modeling CHIP involves the transfer of mutated HSPCs into mice that have not been irradiated, whereby engraftment occurs by competition with native HSPCs (Figure 3b). The study describing this method showed that macrophages derived from the transplanted CHIP-mutant HSPCs readily replace resident kidney macrophages.[82]

In our preprint study, we showed that the *Tet2*-CHIP mouse model is prone to more severe AKI outcomes after ischaemia–reperfusion injury (IRI) or unilateral ureteral obstruction (UUO), which model human ischaemic and obstructive AKI, respectively.[79] The *Tet2*-CHIP mice had more severe reductions in kidney function with higher serum creatinine and blood urea nitrogen at 48-hours and 1-week post-AKI; evidence of more pronounced injury with higher serum kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) levels and structural tubular injury on histologic examination; and more kidney interstitial fibrosis at 28-days post-AKI. CHIP-mutated macrophages producing high levels of IL-1β and other inflammatory cytokines infiltrated the kidneys and maintained their expression of destructive inflammatory and fibrotic mediators until at least 28 days post-AKI.

Pro-inflammatory macrophages have a central, ubiquitous role in CHIP pathogenesis across all mechanistic CHIP studies to date. Data suggesting that experimental CHIP exacerbates AKI in both ischaemic and obstructive mouse models, might indicate that CHIP worsens AKI irrespective of etiology in humans. However, the role of CHIP in specific subtypes of AKI such as acute glomerular injury or drug-induced interstitial nephritis has not been examined. Similarly, it will be important to characterize the role of CHIP across major CKD

aetiologies to determine the magnitude of its compounding effect on disease severity and progression.

CHIP and the cardiovascular system—Several large-scale epidemiological analyses and multiple lines of experimental evidence indicate that CHIP is a risk factor for cardiovascular diseases (CVD) (Tables 1 & 2). CHIP is associated with double the risk of atherosclerotic CVD (ASCVD) independent of traditional risk factors.[83] CHIP has been linked with atherosclerosis in multiple vascular beds throughout the body, as shown in studies evaluating left main coronary artery (LMCA) obstruction, peripheral artery disease and ischaemia from large vessel atherosclerosis[84–87], and confers a higher risk of major adverse cardiovascular events (MACE) in individuals with pre-existing ASCVD.[88] The risk of incident heart failure is also higher in individuals with CHIP with and without coronary artery disease[89], as is the risk of worsening of left ventricular function, hospitalization, and death among those already diagnosed.[90–92] CHIP has additionally been implicated in aortic valve disease prognosis[43,93,94], thoracic aortic aneurysms[95], and doxorubicin-associated cardiotoxicity.[96] Mouse model experiments support a causal role for these associations; *Tet2*-, *Dnmt3a*- and *Jak2*-CHIP aggravated the development of atherosclerosis, and *Tet2*-, *Dnmt3a*-, *Asxl1*-, *Jak2*- and *Ppm1d*-CHIP promoted cardiac fibrosis and heart failure in experimental models (Table 2). Mechanisms linking CHIP to CVD include pathologic activation of inflammasome pathways with increased production of cytokines and chemokines, telomere attrition, and epigenetic ageing.[83,97,98]

CHIP and inflammation in cardiovascular disease—Upregulation of pro-inflammatory cytokine signaling within the myocardium and coronary vessels is a critical pathway of CHIP pathogenesis.[83] In an atherogenic mouse model with experimental *Tet2*-CHIP, atherosclerotic plaque macrophages produced significantly more IL-1β and IL-6, as well as CXC-chemokine ligand 1 (CXCL1), CXCL2 and CXCL3. These cytokines were proposed to promote endothelial cell activation and recruitment of plaque macrophages, and ultimately, atherogenesis.[38,39] Inhibition of IL-1β production with a NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inhibitor (MCC950) reduced plaque burden by ~50% in the *Tet2*-CHIP mouse model, rendering the plaque size similar to that observed in non-mutated control mice.[39] Similarly, in ischaemic and non-ischaemic heart failure mouse models, lowering IL-1β production with MCC950 was effective in preventing *Tet2*-CHIP-mediated exacerbation of heart failure severity.[99] The CANTOS randomized controlled trial tested the efficacy of canakinumab (a monoclonal antibody that blocks IL-1β signaling) in preventing future myocardial infarctions (MI) in individuals with a previous MI and above-normal CRP levels.[100] A secondary analysis of CANTOS found that canakinumab was effective in individuals with *TET2*-CHIP (HR 0.38, 95% CI 0.15–0.96) but not in individuals without CHIP (HR 0.93, 95% CI: 0.78–1.10).[101]

A central role for IL-1β and other inflammatory cytokines in CHIP-exacerbated CVD extends to other subtypes of CHIP. In *Jak2*^{V617F}-CHIP atherogenic mouse models, mutated macrophages produced higher IL-1β, IL-6 and TNF levels, which was associated with enhanced intralesional macrophage proliferation, neutrophil recruitment and plaque instability; inhibition of IL-1β production mitigated the development of this phenotype

compared with control mice.[102,103] Similarly, in heart failure models, higher levels of IL-1β and IL-6 were observed in the macrophages and the myocardia of mice with either *Jak2*^{V617F}- or *Ppm1d*-CHIP compared with control mice.[42,104] Inhibition of IL-1β production with MCC950 was tested in the *Ppm1d*-CHIP model and shown to be effective at mitigating the severity of *Ppm1d*-related heart failure.[104] Pro-inflammatory cytokine elevations were also observed in mouse models of *Dnmt3a*-CHIP and *Tp53*-CHIP[96,105]; however, whether inhibiting IL-1β effectively mitigates the experimental sequelae of CHIP for these and other genes has not yet been reported. Human genetic studies show a protective effect for a common variant in the IL-6 receptor that dampens IL-6 signaling (*IL6R* p.Asp358Ala) on CHIP-associated coronary artery disease and stroke risks, with a greater protective effect for CHIP driven by mutations in genes other than *DNMT3A* (non-*DNMT3A* CHIP).[87,106,107] This finding suggests that inhibiting IL-6 signaling might be a therapeutic strategy that is particularly effective for non-*DNMT3A* CHIP.

In agreement with the proposed central role of inflammatory signaling in CHIP pathology, individuals with CHIP often have signs of elevated peripheral blood levels of pro-inflammatory cytokines; however, the profile of cytokines seen based on the CHIP gene that is mutated is variable.[64] This variability might be partly attributable to differences in the underlying pathways linking CHIP gene mutation to increased inflammation across genes. For example, TET2 deficiency increases IL-1β and IL-6 levels via a few distinct pathways, none of which involve its canonical role in DNA methylation. First, TET2 typically recruits histone deacetylases (HDACs) to IL-6 and IL-1β promoter sites[39,46]; *TET2* truncating mutations impair HDAC-mediated repression of these gene targets.[39] Truncating mutations in either *TET2* or *DNMT3A* not only lead to mitochondrial genome instability, as discussed earlier, but also activate the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway and inflammatory cytokine release.[47] Finally, TET2 deficiency upregulates the expression and activation of NLRP3 inflammasome components, which leads to enhanced cleavage of pro-IL-1β and secretion of mature IL-1β.[39] By contrast, although IL-1β was important in *JAK2*-CHIP-associated atherosclerosis, inhibition of the NLRP3 inflammasome had little effect on mitigating atherosclerotic plaque formation in a murine model.[102] Instead, inhibiting the AIM2 inflammasome — an alternative pathway that also culminates in IL-1β release — was effective in *JAK2*-CHIP.[102] Additionally, in a 2022 report of single cell analyses of peripheral blood cells from individuals with *TET2*- or *DNMT3A*-CHIP, macrophage migration inhibitory factor (MIF), which is a pleiotropic cytokine that promotes leukocyte recruitment, was overexpressed in *TET2*- but not *DNMT3A*-mutated macrophages.[108] Concordantly, a human genetic study found that individuals with a common variant that increases *MIF* expression were at higher risk of *TET2*-CHIP associated ASCVD but not *DNMT3A*-CHIP.[108] These findings underscore differences in the pathways linking CHIP gene mutation to mechanisms of organ injury and damage.

CHIP and telomeres in cardiovascular disease: Telomeres have an important role in CHIP pathogenesis. Telomeres shorten with each cellular division, and cells with critically short telomeres become senescent to maintain genome stability.[109] Shorter leukocyte telomere length is associated with an increased risk of ASCVD, CKD, diabetes and

other chronic diseases.[110–112] Although inflammageing can accelerate telomere shortening, shorter telomeres influence disease risk directly and are not mere signposts of chronic inflammation.[110] In a seeming paradox, genetic variants associated with longer telomeres increase the risk of developing CHIP[113,114], but having CHIP is associated with shorter telomeres. A bidirectional Mendelian randomization study resolved this apparent paradox as it found that longer telomeres increase the lifespan of HSCs, therefore increasing the opportunity for CHIP mutations to occur, whereas the acquisition of a CHIP mutation was associated with subsequent telomere shortening.[97] Importantly, the study showed that CHIP-associated telomere shortening mediates part of the known CVD risk.[97] Of note, shorter telomeres in CHIP-affected cells also influence the risk of other CHIP-associated conditions disease such as CKD.

CHIP and epigenetic ageing in cardiovascular disease: Finally, epigenetic age acceleration (EAA) has been described as a mechanism explaining the increased CVD burden associated with CHIP. DNA methylation markers tend to accumulate steadily with age, and several epigenetic clocks have been developed that can estimate an individual's age based on methylation patterns at specific CpG sites. EAA refers to cases where the inferred epigenetic age is greater than an individual's chronologic age. Increased EAA thus reflects an unfavourable ageing trajectory and has been associated with greater CVD and CKD risk independent of chronological age.[115–118] In two large studies, individuals with CHIP had 2 to 3 years increased EAA on average.[98,119] One study found that individuals with CHIP and EAA were at higher risk of risk of death and CVD compared with individuals without CHIP and without EAA (death: HR 2.90, $p < 4.1 \times 10^{-8}$; CVD: HR 3.24, $p < 9.3 \times 10^{-6}$), whereas individuals with CHIP but without EAA did not have a higher risk of these outcomes.[98] This interaction points to EAA as a modifier (and possibly a mediator) of CHIP-associated CVD risk. Additionally, an epigenome-wide association study (EWAS) prospectively identified differentially methylated CpG sites in CHIP that were concordant in humans and mice; a subset of these sites were shown to promote coronary artery disease risk in subsequent Mendelian randomization studies.[120]

CHIP in diabetes, insulin resistance and obesity—CHIP is more common among individuals with type 2 diabetes[14] and among those with high body-mass index (BMI) and waist-to-hip ratio (WHR).[121,122] Given their cross-sectional nature, these findings might indicate that CHIP promotes the development of diabetes and obesity, or that these conditions stimulate CHIP clonal growth.

Tet2-CHIP promotes age- and obesity-related insulin resistance in mouse models.[32] Using the non-conditioned, non-irradiated CHIP mouse model (see Figure 3b), 6% of circulating white blood cells were $Tet2^{-/-}$ within 2 weeks, and 60% were $Tet2^{-/-}$ at the end of the 84-week observation period. The *Tet2*-CHIP mice developed greater systemic insulin resistance with age despite no differences in total body or fat mass compared with controls. Insulin resistance also developed faster in *Tet2*-CHIP mice fed a high-fat and high-sucrose obesogenic diet. In both the ageing and dietary models, white adipose tissue macrophages produced higher levels of IL-1β in the mice with CHIP compared with controls, and inhibiting IL-1β production with an NLRP3 inflammasome inhibitor mitigated

the insulin resistance. Whether haematopoietic mutations in other CHIP genes contribute to insulin resistance remains to be seen. Germline inactivating mutations in *DNMT3A* cause an overgrowth syndrome with extreme adipogenesis in humans[123], but whether acquired *DNMT3A* CHIP mutations in myeloid cells promote obesity or insulin resistance has not been directly examined.

In addition to promoting inflammation in adipose-resident macrophages, some evidence suggests that *TET2*-CHIP might contribute to diabetes severity via effects in circulating blood cells. Hyperglycaemia inhibits TET2 function in peripheral mononuclear blood cells (PBMCs) by promoting AMP-activated kinase (AMPK)-mediated TET2 phosphorylation and destabilization.[124] PBMCs from individuals with diabetes had global CpG hypomethylation, which is indicative of low TET2 enzymatic activity, and metformin, which is a type 2 diabetes medication that inhibits AMPK, boosted TET2 protein levels and restored CpG methylation. In individuals with an acquired inactivating *TET2*-CHIP mutation in one allele, hyperglycaemia could lead to functional depletion of TET2 protein produced by the other allele and exacerbate PBMC TET2 deficiency. Whether this further TET2 depletion from hyperglycaemia would manifest as diabetes complications, including exacerbation of diabetic kidney disease, in those with CHIP and uncontrolled hyperglycaemia, remains to be determined.

A 2023 report linked CHIP to an increased risk chronic liver disease, with higher odds of non-alcoholic steatohepatitis (NASH) in particular, which is an entity characterized by inflammation of fatty deposits in the liver.[66] Inflammation and fibrosis in liver samples from individuals with CHIP, as well as in the livers of a NASH *Tet2*-CHIP mouse model, were more severe than in healthy individuals or control mice.[66] *Tet2*$^{-/-}$ macrophages from these mice infiltrated the liver and replaced endogenous Kupffer cells, expressed high levels of pro-inflammatory cytokines, and activated fibrotic responses in neighbouring hepatic stellate cells.[66] Inhibition of IL-1β signaling in these mice abrogated the NASH phenotype, and individuals with the *IL6R* p.Asp358Ala genetic variant were protected against CHIP-related liver disease, highlighting once again the central role of inflammation in mediating the link between CHIP, adiposity and organ damage.

Conversely, obesity and adipose tissue-related inflammation have been associated with an increased risk of CHIP clonal expansion. Rapid CHIP clonal expansion was observed in mouse models of diabetes and obesity[32,122], and obesity-related inflammation and insulin resistance were identified as risk factors for CHIP clonal expansion in longitudinal studies of individuals with obesity.[122,125,126] Obesity additionally promotes the accumulation of adipocytes in the bone marrow, which is also associated with CHIP clonal expansion.[52,122] Elevated calcium signaling in *Tet2*-mutated HSPCs might drive obesity-related clonal expansion in mice, and blocking calcium release with nifedipine (a calcium-channel blocking anti-hypertensive medication) was effective at dampening clonal expansion of HSPCs with *Tet2*, *Dnmt3a*, *Asxl1*, or *Jak2* CHIP mutations *in vivo*.[122] The clonal expansion-blocking effect of nifedipine was synergistically enhanced when combined with inhibition of mitochondrial glucose sensitivity with metformin, inhibition of Nlrp3 inflammasome activation with MCC950, or blocking of the IL-1 receptor with anakinra.

A large observational study identified that an unhealthy diet (defined as a lower-than-median intake of fruits and vegetables and higher-than-median intake of unhealthy elements including red meat, processed food and added salt) was linked to higher CHIP prevalence[127], suggesting a possible role for dietary interventions and weight loss in mitigating CHIP and its adverse effects. Concordantly, a 2023 study showed that individuals who underwent bariatric surgery had slower clonal expansion rates than individuals with obesity who did not undergo bariatric surgery.[126] Additionally, boosting residual TET2 activity with ascorbate (also known as vitamin C), which is a co-factor of TET2, is hypothesized to partly mitigate the effects of inactivating CHIP mutations, though this possibility has not been tested clinically.[128,129]

CHIP and gout—Hyperuricemia and gout are common in patients with CKD[130]. In a cross-sectional study of the US population, gout was eight times more common in individuals with eGFR < 60 ml/min/1.73 m^2 than in those with eGFR ≥ 90 ml/min/1.73 m^2.[131] *TET2*-CHIP has been associated with increased risk of gout in an observational cohort study.[45] *Tet2*-CHIP mice that received monosodium urate had elevated IL-1β cytokine levels and more severe gouty lesions (specifically, paw oedema) than wild-type controls. Both genetic deletion of *Nlrp3* and pharmacological inhibition of NLPR3 prevented gouty lesion formation, suggesting a central role for the IL-1β inflammatory pathway in *TET2*-CHIP-associated gout risk.[45]

CHIP and osteoporosis—Bone demineralization and extraosseous calcification are cardinal features of CKD-related bone mineral disease[132], and fractures are a common cause of morbidity and mortality in the CKD population.[133] In the UK Biobank, CHIP was associated with lower bone mineral density and increased osteoporosis risk.[134] Moreover, irradiated mice receiving bone marrow transplants of HSPCs with inactivating *Tet2* or *Dnmt3a* mutations had significant reductions in femoral bone mass. [134] Osteoclasts, which are a type of terminally differentiated macrophage, had higher bone demineralizing activity in the *Dnmt3a*-CHIP mouse model, primarily owing to increased inflammatory signaling from neighbouring bone-marrow resident monocytes. These findings might have important implications for bone health in individuals with CKD and CHIP.

CHIP and autoimmunity—CHIP seems to be more common among individuals with certain autoimmune diseases including rheumatoid arthritis and vasculitis.[135–137] In a study of 112 patients with anti-neutrophil antibody (ANCA)-associated vasculitis (AAV), CHIP was present in 30% of patients (compared with 13% of age-matched healthy individuals). Curiously, *TET2*- and *DNMT3A*-mutated neutrophils from patients with AAV were hyporesponsive to ANCA stimulation, suggesting that CHIP might dampen disease severity.[136] CHIP-mutated neutrophils have impaired neutrophil extracellular trap formation in the setting of infection[48], and the same might occur in the setting of autoimmune disease. Rare cases of severe adult-onset autoinflammatory conditions caused by secondary acquired mutations in HSPCs that already have a CHIP mutation have also been reported. In these cases, the mutant cells were thought to undergo clonal expansion as a result of *TET2* (CHIP) mutations, which led to severe autoinflammation owing to secondary variants in either

NLRC4 or *UBA1*.[138,139] However, the full spectrum of implications for CHIP mutations in autoimmune disease requires further investigation.

CHIP and infection—CHIP is associated with a higher risk of all-cause bacterial infections, viral infections, and sepsis.[140] Targeted studies have reported a higher prevalence of CHIP in individuals living with human immunodeficiency virus (HIV) compared to those without HIV.[141,142] Whether CHIP predisposes to SARS-CoV-2 infection or the severity of COVID-19 is unclear, as studies have reported mixed findings[143–146] (reviewed in[147]). Given that individuals with kidney disease are at higher risk of infection, CHIP might be a compounded risk factor in this setting. Whether infections that affect kidney transplant recipients (for example, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and BK virus infections) are more likely in patients with CHIP remains unknown.

CHIP and cognitive function—A 2023 study identified CHIP as a protective factor for Alzheimer's disease (AD) dementia. Individuals with CHIP had lower rates of AD than matched controls without CHIP, and a causal association was inferred using Mendelian randomization analysis.[148] Of note, CHIP mutations detected in peripheral blood cells were also identified in microglia from brain autopsy samples of older individuals without AD. This finding suggests that monocyte-derived macrophages with CHIP mutations engraft in the brain and replace resident microglia (similar to what occurs with Kupffer cells in the liver). Microglia are the brain's specialized macrophages that have a key role in AD pathogenesis[149] and it is possible that the CHIP-mutated microglia attenuate the risk of AD, although this mechanistic link was not established in the study.[148] Cognitive impairment is common in CKD and patients have higher rates of vascular and AD dementias compared with the general population.[150,151] Microglia seem to have an important role in regulating brain oxidative stress and healing after microvascular disruption in CKD.[152] Whether microglial CHIP mutations impact cognitive function in patients with CKD more broadly, and whether they have a protective or detrimental role, remains to be determined.

CHIP in the clinic: risk factors and therapies

CHIP mutations occur in the bone marrow with age: nearly everyone aged 50 or older will have at least one affected hematopoietic stem cell, although most stem cells will not produce a clonal population of circulating cells large enough to be labeled as CHIP.[153] Age is the strongest correlate of CHIP prevalence (Figure 1d) and, in cross-sectional sectional studies, CHIP is more common among men and less common in certain ancestral groups (for example, in individuals of Hispanic and Latino ancestry).[59] Chronic inflammation — such as that observed in the setting of chronic infection or obesity — is a key driver of clonal expansion.[50–55] The prevalence of CHIP increases as eGFR decreases[73,154], although the causality of this relationship remains unclear. CHIP seems to be a risk factor for eGFR decline and CKD progression[74,76], but CKD-associated inflammation might promote CHIP clonal expansion. Of note, smoking is strongly associated with having CHIP (particularly *ASXL1*-CHIP[155]), although whether this association is primarily due to mutagenesis or promotion of clonal expansion remains unclear. Cytotoxic chemotherapy is associated with a rise in mutations in DNA damage repair (DDR) enzymes such as *TP53* and *PPM1D*.[70] For example, platinum-based drugs promote treatment-related clonal hematopoiesis primarily

because clones with DDR mutations are resistant to the selective constraint posed by the chemotherapy.[156] Additionally, germline genetic variants in at least 33 distinct loci have been associated with CHIP or specific gene subtypes of CHIP[64,144], including a common variant in *TCL1A* (rs2887399) that is associated with a slower rate of clonal expansion in non-*DNMT3A* CHIP.[157]

Understanding the risk factors for CHIP is important when considering preventative or therapeutic measures. The long-term translational goal for the CHIP field is to identify populations most harmed by CHIP and scenarios where offering treatment for CHIP could outweigh the risks. Pre-clinical work points to potential therapies targeting the inflammatory state conferred by CHIP (for example, with IL-1β or IL-6 blockers) as a potential approach to both dampen clonal expansion and reduce the end-organ damage. However, these treatments are associated with risk owing to the central role of these cytokines in the innate immune system, and it is unclear what dosing regimen might be beneficial. Common medications including metformin and nifedipine show promise to potentially reduce obesity-related CHIP clonal expansion given results in mouse models.[122] However, randomized controlled trials will be required to assess the value of these candidate therapies in patients with CHIP.

Specialized clinics have been developed at a few US centres to guide the management of patients in whom CHIP has been detected incidentally.[158] Their current recommendations center around optimizing modifiable cardiovascular risk factors.[158] Additionally, newer risk stratification tools such as the CHRS enable the identification of patients who should be more closely monitored for transformation to myeloid cancer.[63]

Conclusions

CHIP was first defined less than ten years ago[58] and, since then, several research studies have revealed its effects on multiple organ systems. As it pertains to the kidney, CHIP has been associated with progressive kidney function decline and AKI (Figure 4), with evidence from epidemiological studies and mouse models supporting a direct role for CHIP in kidney pathology. Future work will need to identify mechanisms driving these nascent kidney disease associations, and the spectrum of harm in patients with CKD, including the risk of cardiovascular disease and CKD-related anaemia. Other key questions include whether certain aetiologies of CKD are more vulnerable to the harmful effects of CHIP, and whether certain subtypes of CHIP are more harmful to the kidneys.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Glossary terms

VEXAS syndrome

First described in 2020, VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is a severe, adult-onset autoinflammatory disease caused by acquired mutations in the ubiquitin ligase enzyme gene (*UBA1*) in circulating blood cells

Variant allele fraction

The variant allele fraction (VAF) is the proportion of sequencing reads that contain the variant, which serves as an estimate of the fraction of cells containing the variant (for autosomal chromosomes and X-chromosomes in females, VAF × 2 = the cell fraction)

Passenger variants

Passenger variants are acquired genetic changes that accumulate in cells over time but are not expected to affect cell fitness nor drive clonal expansion, in contrast to driver mutations

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Box 1.

Key pro-inflammatory pathways in chronic inflammation

Immune responses are coordinated by intracellular communication between white blood cells and tissues. Pro-inflammatory cytokines are the messengers that localize a threat or injury and recruit the appropriate cellular responders. IL-6 is the central ‘warning’ cytokine that is produced by immune and structural cells at the site of tissue injury.[163] IL-6 acts on a variety of cell types: it stimulates the production of acute phase reactants such as C-reactive protein (CRP) and fibrinogen by the liver, promotes B-cell antibody synthesis and effector T-cell maturation, and engages local structural cells (for example, fibroblasts and epithelial cells) in wound repair.[163] Other key pro-inflammatory cytokines such as IL-1β and tumor necrosis factor (TNF) can also upregulate IL-6 levels. Mature IL-1β is produced and secreted by monocytes and macrophages upon activation of NOD-, LRR- and pyrin domain-containing 3 (NLRP3) or other inflammasomes by pattern response recognition of pathogen-associate or damage-associated molecular patterns (PAMPs and DAMPs, respectively).[164] Similar to IL-6, IL-1β stimulates proliferation and activity of neighbouring structural cells as well as adaptive immune cells, and it also induces fever and promotes local production of reactive oxygen species and nitric oxide.[164] TNF is mainly produced by monocytes and macrophages, and has roles that overlap with IL-1β, such as fever and non-immune cell activation, as well as other roles including stimulating phagocytosis and promoting neutrophil recruitment.[165] Leukocyte recruitment is also achieved through a variety of chemokines, including the IL-8 family of cytokines (for example, CXC-chemokine ligand 1 (CXCL1), CXCL2 and CXCL3).[166]

This inflammatory response is typically transient, but in the setting of unresolved injury, cytokine elevations can persist, leading to maladaptive chronic inflammation. Therapies targeting the aforementioned cytokines are used in autoimmune diseases (for example, TNF inhibitors in inflammatory bowel disease), and the use of these agents (such as canakinumab (anti-IL-1β) and ziltivekimab (anti-IL-6)) is being considered in high-inflammation chronic disease states, including cardiovascular disease and chronic kidney disease.[100,167–169]

Key points

- Clonal hematopoiesis of indeterminate potential (CHIP) is a common, acquired condition wherein mutated white blood cells form an expanded clonal population in the blood and cause chronic organ damage through dysregulated inflammation.
- CHIP has been associated with a greater risk of acute kidney injury (AKI) and impaired recovery from AKI in human population cohorts and in mouse models, as well as loss of kidney function in the general population and in those with chronic kidney disease.
- In addition to its direct effects on the kidney, CHIP predisposes individuals to several conditions that impact kidney health, including cardiovascular disease, gout, osteoporosis and insulin resistance.
- CHIP affects 10–20% of individuals aged 65 and older; other than age, risk factors include smoking, male sex, chronic inflammation, cytotoxic therapies and certain inherited genetic variants.
- In preclinical models, cytokine blockade strategies mitigate many of the pathologic effects of CHIP; these strategies are being evaluated in humans.

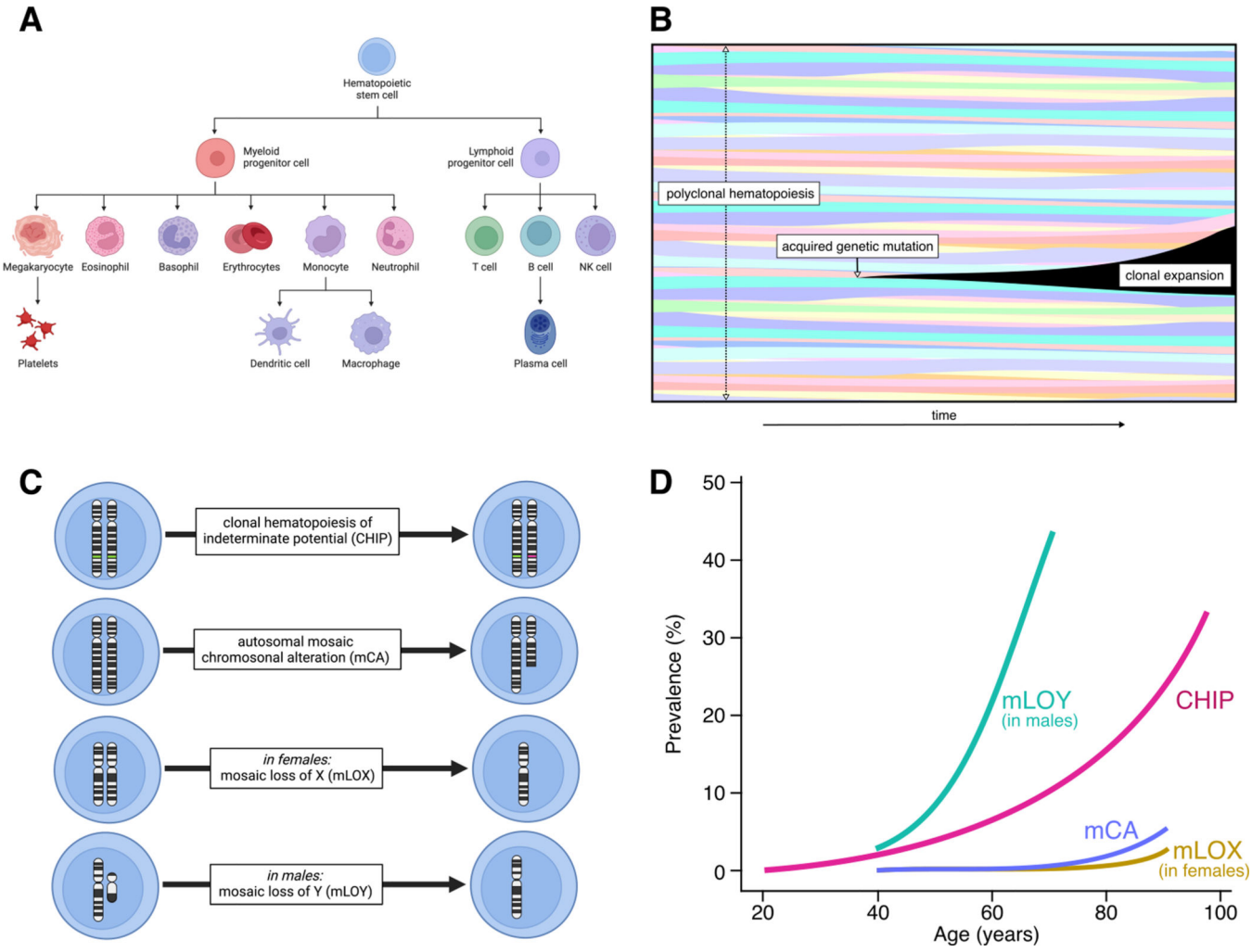
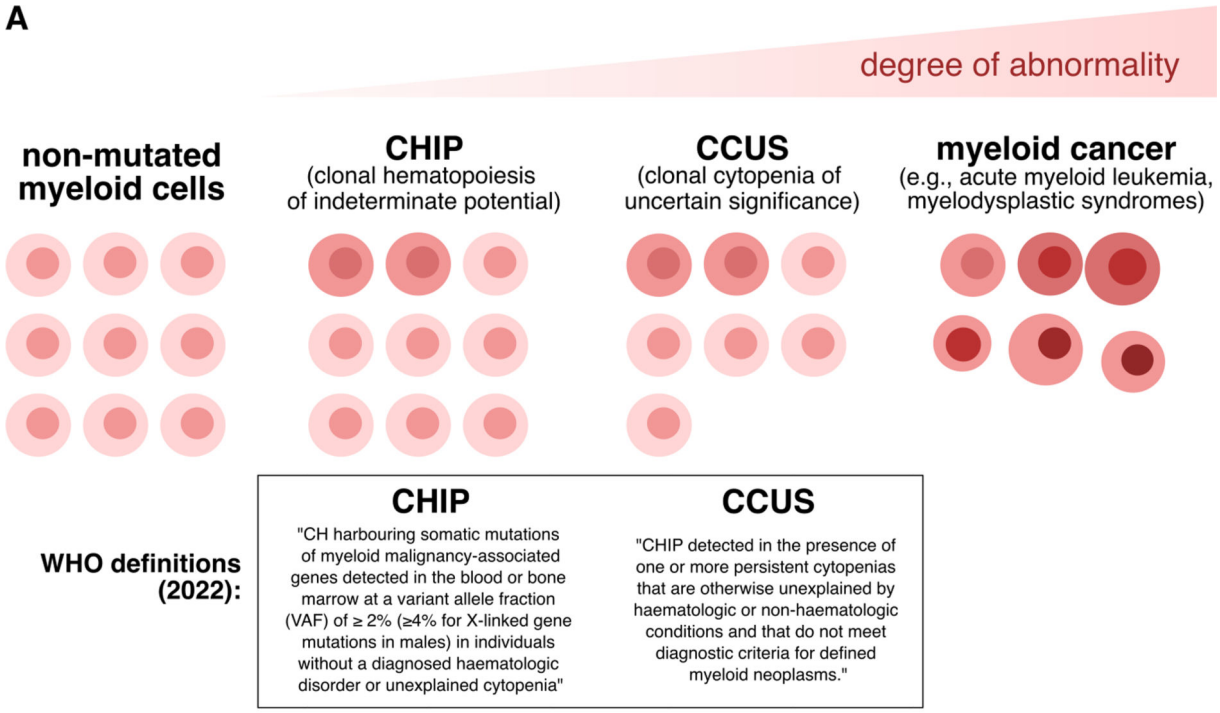


Figure 1. Subtypes of clonal haematopoiesis

a| With each cell division, haematopoietic stem and progenitor cells (HSPCs) can either self-renew, producing genetically identical HSPCs, or differentiate into daughter cells of the myeloid or lymphoid lineage. b| Haematopoiesis is normally polyclonal, wherein ~20,000 HSPCs contribute roughly equally to the circulating pool of daughter cells. Clonal hematopoiesis occurs when an HSPC acquires a genetic change that confers a proliferative advantage, leading to an overrepresentation of its progeny in the circulating pool of blood cells. c| Two major types of clonal haematopoiesis are recognized, defined by the type of genetic change that is driving clonality: CHIP (driven by point mutations or small indels in myeloid cancer-related genes) and mosaic chromosomal alterations (mCAs; driven by gains or losses of partial or whole chromosomes, or copy-neutral loss-of-heterozygosity). mCAs can further be subdivided into autosomal mCAs, mosaic loss of X (in genetic females) and mosaic loss of Y (in genetic males). d| The prevalence of each type of clonal haematopoiesis increases with age. Prevalence estimates for CHIP are approximated from ref.[162] (variant allele fraction ≥ 2%). Prevalence estimates for autosomal mCAs are approximated from ref.[162] (cell fraction ≥ 10%). Prevalence estimates for mLOX are approximated from ref.[18] (cell fraction ≥ 5%).[18] Prevalence estimates for mLOY based on ref.[56,57].



B

Clonal hematopoiesis risk score (CHRS)

From Weeks *et al.*, *NEJM Evidence,* 2023

Prognostic variable	0.5	1	1.5	2	2.5
Single *DNMT3A*	Present	Absent			
High-risk mutation		Absent			Present
Mutation number		1		≥2	
Variant allele fraction		<0.2		≥0.2	
Red cell distribution width		<15			≥15
Mean corpuscular volume		<100			≥100
Cytopenia		CHIP	CCUS		
Age (years)		<65	≥65		

Figure 2. The spectrum of clonal myeloid disease

Definitions of clonal hematopoiesis of indeterminate potential (CHIP), clonal cytopenia of uncertain significance (CCUS) as they compare to myeloid cancer. CHIP refers to a clonal blood cell population resulting from acquired mutations in myeloid malignancy-associated genes that is detected at a variant allele fraction (VAF) of ≥ 2%.[58] When an individual with a CHIP mutation also has an otherwise unexplained cytopenia, this is referred to as a clonal cytopenia of undetermined significance (CCUS).[63]

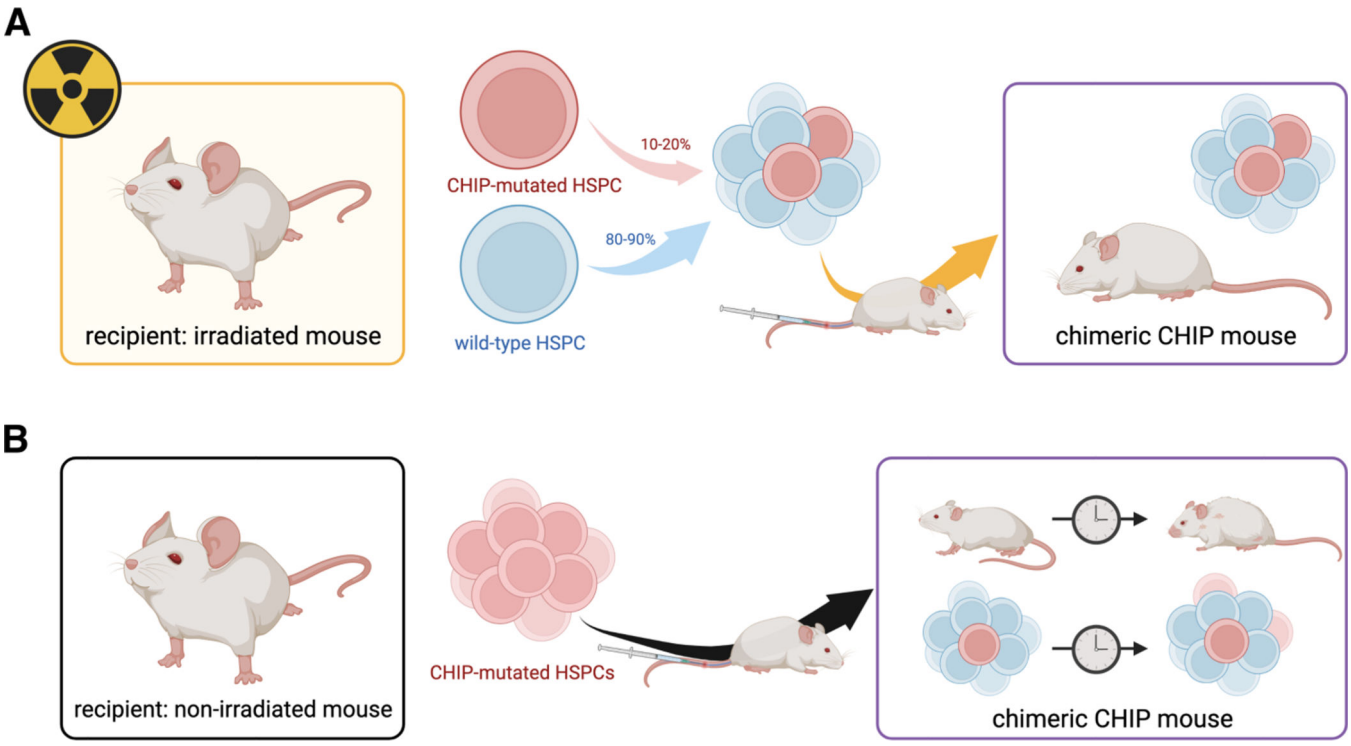


Figure 3. CHIP mouse model systems.

a| The classic clonal hematopoiesis of indeterminate potential (CHIP) mouse model is based on transplantation of chimeric bone marrow — containing a fraction of haematopoietic stem and progenitor cells (HSPCs) with CHIP mutations and a fraction of cells without CHIP mutations — into mice that have undergone lethal irradiation of their bone marrow. Control mice typically receive a bone marrow transplant that consists entirely of non-mutated HSPCs. Recipient mice might have germline mutations and/or be exposed to dietary or other environmental exposures to model a phenotype of interest. b| The non-conditioned mouse model involves injecting CHIP-mutated HSPCs into mice that have not been irradiated. Engraftment and clonal expansion of HSPCs in the recipient bone marrow occurs over time. This radiation-sparing method is considered optimal for long-term experiments.[81]

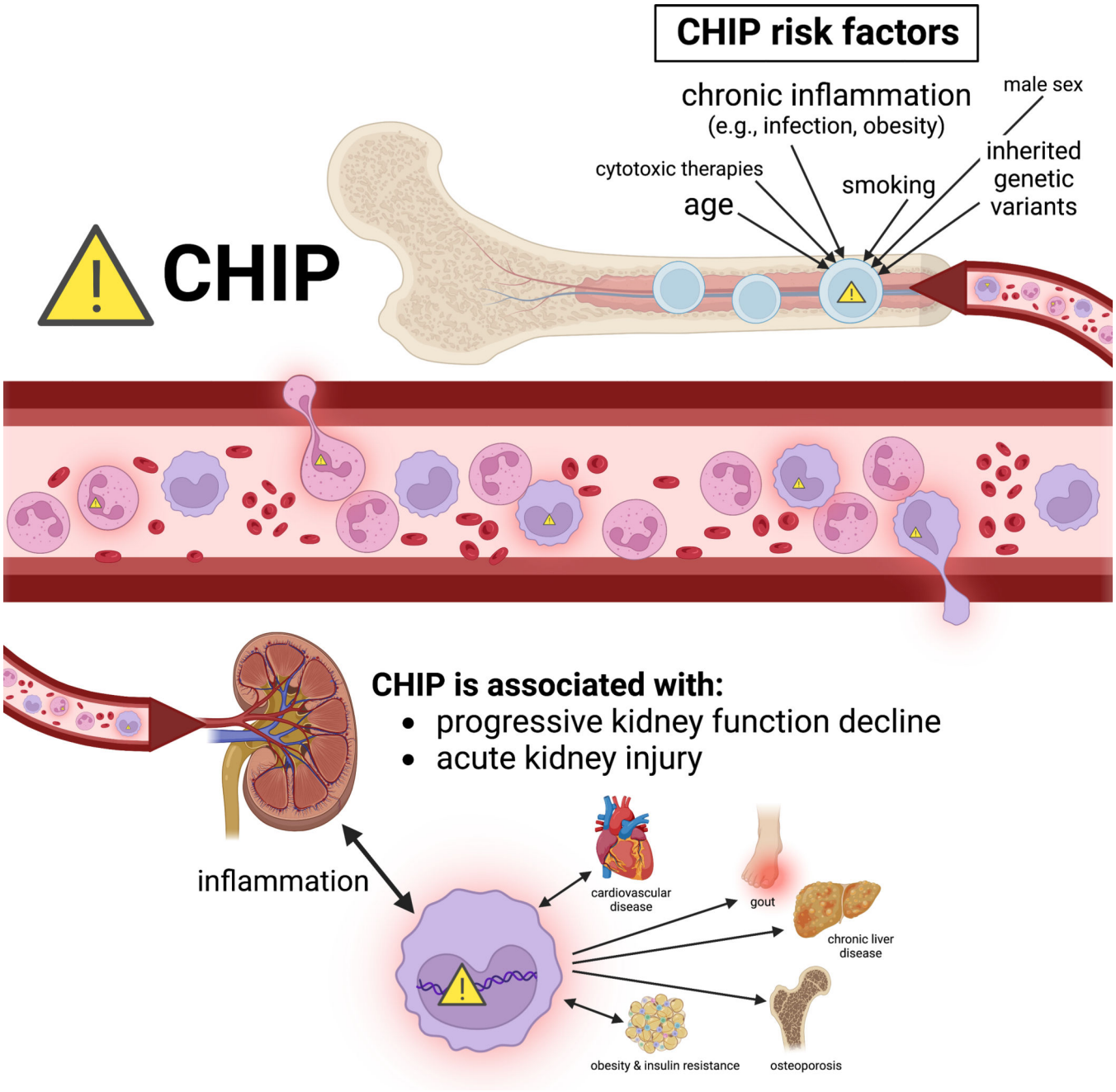


Figure 4. Conceptual model of the role of CHIP in kidney health.

CHIP is an acquired inflammatory condition associated with acute kidney injury, progressive decline of kidney function, as well as several other conditions that can affect kidney health, including cardiovascular disease, gout, chronic liver disease, osteoporosis, obesity and insulin resistance. Mutagenesis of a myeloid cancer-associated gene is the initiating event in CHIP, and several risk factors for subsequent clonal expansion have been identified, including age, smoking, male sex, chronic inflammation, cytotoxic therapies and certain inherited genetic variants.

Table 1.

Key observational studies in humans linking CHIP to CVD

Phenotype	Outcome	Population (N)	Risk (95% CI)	Ref.
Atherosclerotic heart disease	CVD	22 population-based cohorts (17,182)	HR 2.0 (1.2–3.4)	14
		Patients undergoing total hip arthroplasty (200)	OR 2.4 (1.2–4.6)	135
		'Oldest-old' persons in two population-based cohorts of (1,794)	HR 1.6 (1.3–3.2)	159
	CAD (MI or revascularization)	Nested case–control study (1,010)	HR 1.9 (1.4–2.7)	38
	Early onset MI (before age 50)	2 population-based cohorts (3,336)	OR 4.0 (2.4–6.7)	38
	Left main coronary artery stenosis	Patients undergoing coronary artery catheterization (1,149)	OR 1.8 (1.2–2.7)	84
Heart failure	Incident HF	5 population-based cohorts (57,597)	HR 1.3 (1.1–1.4)	89
	Death or HF hospitalization	Patients with stable HFrEF and coronary revascularization ≥ 3 months prior, NYHA class II or III (200)	HR 2.1 (1.1–4.0)[a]	90
	Death or HF hospitalization	Patients with stable HFrEF of any cause (67)	HR 3.8 (1.8–8)[a]	92
	Death		HR 2.8 (1.3–5.9)[a]	92
	HF-related death or hospitalization		HR 4.4 (2.2–9)[a]	92
Peripheral artery disease	Incident PAD	2 population-based cohorts (50,122)	HR 1.7 (1.3–2.1)	85
Stroke	Incident ischemic stroke	22 population-based cohorts (17,182)	HR 2.6 (1.4–4.8)	14
	Incident stroke	8 prospective cohorts and biobanks (78,752)	HR 1.14 (1.03–1.27)[b]	86
	Recurrent stroke, MI, or death	Patients with first-ever ischaemic stroke (581)	HR 1.6 (1.04–2.3)	87
Aortic stenosis	Medium-term all-cause mortality	Patients with severe aortic stenosis undergoing TAVI (279)	HR 3.1 (1.2–8.1)[a]	93
	Long-term all-cause mortality	Patients with severe aortic stenosis undergoing TAVI (453)	HR 1.43 (1.01–2.01)[a]	94
Aortic aneurysms	Incident thoracic aortic aneurysms	UK Biobank participants (452,093)	HR 12.8 (4.8–34)[c]	95

CAD, coronary artery disease; CHIP, clonal haematopoiesis of indeterminate potential; CVD, cardiovascular disease; HF, heart failure; HFrEF: heart failure with reduced ejection fraction; HR, hazard ratio; LOF: loss-of-function; MI, myocardial infarction; NYHA, New York Heart Association; OR, odds ratio; PAD, peripheral artery disease; TAVI, transfemoral aortic valve implantation.

[a] *DNMT3A* or *TET2* mutations examined only.

[b] *DNMT3A, TET2 or ASXL1* mutations examined only.

[c] $JAK2^{V617F}$ mutations examined only.

Table 2.

Key experimental studies in mice linking CHIP to CVD

Phenotype	CHIP subtype	Findings	Ref.
Atherosclerotic heart disease	*Tet2* LOF	*Ldlr*$^{-/-}$ mice that received a BMT of *Tet2*$^{-/-}$ or *Tet2*$^{+/-}$ HSPCs and were subsequently fed an atherogenic diet in two independent studies had larger atherosclerotic plaques in the aortic root. Inhibiting IL-1β production with an NLRP3 inflammasome inhibitor abrogated the development of atherosclerosis in this mouse model.	38,39
	Dnmt3a LOF	*Ldlr*$^{-/-}$ mice that had received a BMT of *Dnmt3a*$^{-/-}$ HSPCs and were subsequently fed an atherogenic diet had larger atherosclerotic plaques in the aortic root.	105
	Jak2^{V617F}	*Ldlr*$^{-/-}$ mice that received a BMT of *Jak2*^{V617F} HSPCs and were subsequently fed an atherogenic diet in two independent studies had larger atherosclerotic plaques in the aortic root. Genetic inactivation of the AIM2 inflammasome (*Aim2*$^{-/-}$) or treatment with anti-IL-1β antibodies in these mice decreased intralesional macrophage proliferation and improved plaque stability.	102,103
Heart failure	*Tet2* LOF	Mice that received a BMT of *Tet2*$^{-/-}$ or *Tet2*$^{+/-}$ HSPCs and subsequently underwent one of two surgical procedures to induce heart failure (LAD ligation or transverse aortic constriction) had larger myocardial infarct size, poorer post-ischaemic remodeling, and lower ejection fractions. Inhibiting IL-1β production with an NLRP3 inflammasome inhibitor abrogated the development of heart failure in this mouse model.	99
		Aged, non-irradiated[a] mice who had received a BMT of *Tet2*$^{-/-}$ HSPCs developed spontaneous cardiac fibrosis and hypertrophy.	82
		Mice that received a BMT of HSPCs with CRISPR/Cas9-guided inactivation of *Tet2* and subsequently received an angiotensin II infusion had greater cardiac fibrosis and hypertrophy.	40
	Dnmt3a LOF	Mice that received a BMT of HSPCs with CRISPR/Cas9-guided inactivation of *Dnmt3a* and subsequently received an angiotensin II infusion had greater cardiac fibrosis and hypertrophy.	40
	Asxl1 LOF	Mice that received a BMT of *Asxl1*$^{+/-}$ HSPCs who subsequently underwent either LAD ligation or angiotensin II infusion to induce heart failure had lower ejection fraction and greater cardiac fibrosis.	160
	Jak2^{V617F}	Mice that received a BMT of *Jak2*^{V617F} HSPCs who subsequently underwent one of two surgical procedures to induce heart failure (LAD ligation or transverse aortic constriction) had larger myocardial infarct size, poorer post-ischaemic remodeling and lower ejection fractions.	42
	Ppm1d LOF	Mice that received a BMT of HSPCs with CRISPR/Cas9-guided inactivation of *Ppm1d* and subsequently received an angiotensin II infusion had greater cardiac fibrosis and hypertrophy.	104
Doxorubicin-induced cardiotoxicity	*Tp53* LOF	After infusion of doxorubicin, both irradiated mice that had received a BMT of *Tp53*$^{+/-}$ HSPCs and non-irradiated[†] mice that had received a BMT of *Tp53*^{R270H} or *Tp53*$^{+/-}$ HSPCs had LV functional impairment, LV wall thinning and cardiac fibrosis.	96
Aortic aneurysms	*Jak2*^{V617F}	*Apoe*$^{-/-}$mice that received a BMT of *Jak2*^{V617F} HSPCs and subsequently received an angiotensin II infusion had greater abdominal aorta diameter and more abdominal aortic aneurysms.	161

AIM2, absent in melanoma 2; BMT, bone marrow transplant; CHIP, clonal haematopoiesis of indeterminate potential; CRISPR-Cas9, clustered regularly interspaced short palindromic repeats/clustered regularly interspaced short palindromic repeat–associated 9; CVD, cardiovascular disease; HSPCs, haematopoietic stem and progenitor cells; LAD, left anterior descending; LOF, loss-of-function; LV, left ventricular; NLRP3, Nod-like receptor family pyrin domain containing 3.

[a]See Figure 3 for details of irradiated and non-irradiated mouse models of CHIP.